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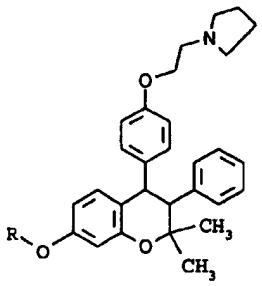
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING 3,4-DIARYLCHROMANS IN LOW DOSE



(I)

(57) Abstract

New pharmaceutical formulations for oral administration comprising a low dose of certain 3,4-diarylchromans of formula (I) which are useful in reducing bone loss.

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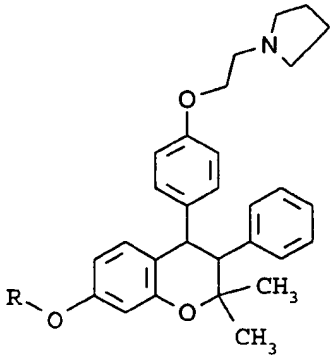
TITLE

Pharmaceutical composition comprising levormeloxifene in low dose.

FIELD OF THE INVENTION

This invention relates to new pharmaceutical formulations for oral administration comprising a low dose of certain 3,4-diarylchromans of formula I, or a pharmaceutically acceptable salt thereof.

The 3,4-diarylchromans of formula I



(I)

wherein R is C_{1-6}alkyl, and pharmaceutically acceptable salts thereof are known to be useful in reducing bone loss.

BACKGROUND OF THE INVENTION

Bone remodeling is the dynamic process whereby skeletal mass and architecture are renewed and maintained. This renewal and maintenance is a balance between bone resorption and bone formation, with the osteoclast and the osteoblast considered the two key participants in the remodeling process. The osteoclast initiates the remodeling cycle by resorbing a cavety in the bone which is subsequently refilled when the osteoblast synthesizes and deposits new bone matrix into the excavation. The activi-

ties of osteoclast and osteoblast are regulated by complex interactions between systemic hormones and the local production of growth factors and cytokines at active remodeling sites

Imbalances in bone remodeling are associated with such conditions as osteoporosis, Paget's disease, and hyperparathyrodism. Osteoporosis, characterized by a decrease in the skeletal mass, is one of the most common diseases of postmenopausal women and is often the cause of debilitating and painful fractures of the spine, hip and wrist.

The costs of osteoporosis, both personal and financial, are enormous. In 1984, 145,000 in-patient fracture reductions and 107,000 hip arthroplasties and replacements were performed on American women over 65 years of age. Among patients who lived alone prior to hip fracture, 15% to 20% required long-term care as a result of the fracture and one year after the fracture had still not regained their independence. The total financial cost of osteoporosis treatment, including fractures, in the United States in 1986 was 7-10 billion dollars (Peck et al., Am.J.Med. 84:275-282, 1988).

Bone loss associated with osteoporosis has been arrested by the administration of exogeneous estrogens. To be effective, estrogen therapy must begin within a few years of the onset of menopause, and should continue for 10 to 15 years, according to Thorneycroft (Am.J.Obstet.Gynecol. 160:1306.1310m 1989), While there are several different types of estrogens, 17-β-estradiol is the primary estrogen found naturally occurring in premenopausal women and is often the compound of choice for therapetic use. At the recommended dose, however, there are significant side effects, the most distrubing being the well-established correlation of estrogen therapy with endometrial and brest cancers. The incidence of carcinoma is both dose-dependent and duration-dependent.

Avoidance of the cancer risk has been achieved by the concomitant use of a progestogen with estrogen. This combination, however, causes menses to return, which many women find unacceptable. A further disadvantage is that the long-term effects of the progestogen have not been fully determined. Thus, a large population of women require alternatives to hormone replacement therapies that can safely prevent the rapid bone loss that accompanies the menopause.

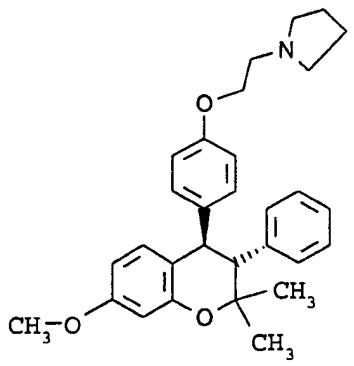
The formula I compounds are described in U.S. Patent No. 5,280,040. This patent describes the preparation of these compounds, as well as their use in reducing bone loss. The preparation of pharmaceutical compositions is also described.

Centchroman, which is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman, is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent No. 4,447,622; Singh et al., Acta Endocrinal (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783). Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical agent expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

Levormeloxifene, (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, is a particular preferred compound from this series of 3,4-diarylchromans. Levormeloxifene may be used in human and veterinary medicine for the regulation of bone metabolism. It may be used, for example, in the treatment of patients suffering from bone loss due to osteoporosis (including post-menopausal osteoporosis and glucocorticoid-related osteoporosis), Paget's disease,

hyperparathyroidism, hypercalcemia of malignancy and other conditions characterized by excessive rates of bone resorption and/or decreased rates of bone formation.

The 3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent No. 3,340,276 to Carney et al., U.S. Patent No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. The resolvation of (+/-) - 3,4-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in its optical antipodes is described in U.S. Patent No. 4,447,622 incorporated herein by reference. Example 1 of U.S. Patent No. 4,447,622 describes the preparation of the minus enantiomer, shown by formula II :



(II)

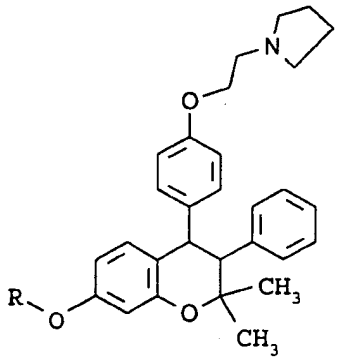
(In this specification, the compound of formula II is referred to as levormeloxifene.) In example 2 of U.S. Patent No. 4,447,622, levormeloxifene is obtained as the free base and the hydrochloride salt.

The compounds of formula I may be administered as pharmaceutically acceptable salts. A particularly useful pharmaceutically acceptable salt of levormeloxifene is the hydrogen fumarate salt (in this specification, this compound is referred to as levormeloxifene fumarate.). This salt form is prepared by dissolving fumaric acid and (-) -3R,4R- trans - 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in a common solvent such as e.g. methanol, and crystallizing the resulting salt from the solution.

In WO 94/20098 the therapeutic doses of 3,4-diarylchromans for reducing bone loss, in particular, treatment of osteoporosis is mentioned to be in the range from 0.01-50 mg/kg/day, and the most preferred range being 0.1-5.0 mg/kg/day.

DESCRIPTION OF THE INVENTION

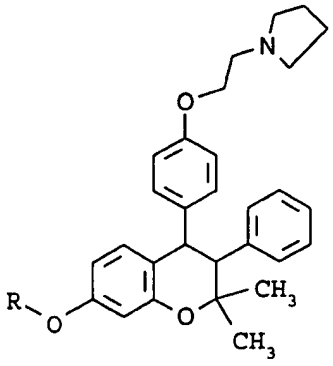
The present invention provides a pharmaceutical composition of a dosage form for oral administration comprising a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof. The amount of compound of formula I needed is very low.

The present invention provides a pharmaceutical composition of a dosage form for oral administration comprising a compound of formula I

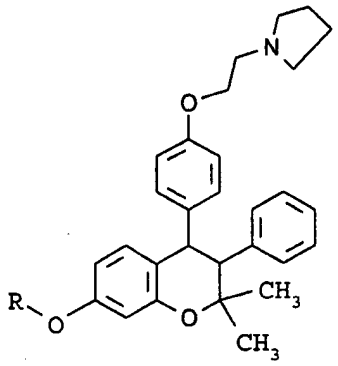


(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, in an amount of between about 0.01 and 0.65 mg/day. Preferably the dosage form is a unit dosage form.

The compound of formula I may be used in an amount of between about 0.01 and 0.65 mg/day, in the treatment of patients suffering from bone loss due to osteoporosis (including post-menopausal osteoporosis and glucocorticoid-related osteoporosis), Paget´s disease, hyperparathyroidism, hypercalcemia of malignancy and other conditions characterized by excessive rates of bone resorption and/or decreased rates of bone formation or in patients susceptible to bone loss. In one particular embodiment the pharmaceutical composition is for preventing bone loss. In another particular embodiment the pharmaceutical composition is for reducing bone loss. In a particular embodiment the bone loss is due to osteoporosis.

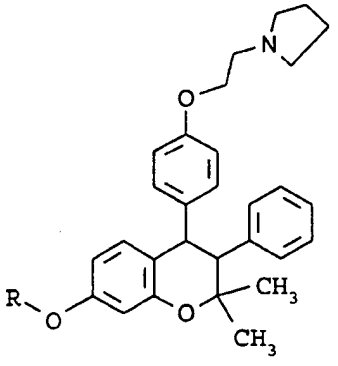
The present invention also relates to the use of a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, in an amount of between about 0.01 and 0.65 mg/day, for the preparation of a pharmaceutical composition of a dosage form, preferably a in unit dose form, for oral administration for reducing bone loss. In one embodiment hereof the bone loss is due to osteoporosis.

The present invention furthermore relates to a method for reducing bone loss in a patient comprising administering to the patient suffering from bone loss a pharmaceutical composition in oral dosage form, preferably unit dose form, comprising a bone loss inhibiting amount of between about 0.01 and 0.65 mg/day of a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof. In one embodiment hereof the bone loss is due to osteoporosis.

In an embodiment of the present invention the composition comprises the compound of formula I, or a pharmaceutically acceptable salt thereof, in an amount of between about 0.05 and 0.65 mg/day. In another embodiment the amount is between about 0.05 and 0.09 mg/day. In a still other embodiment the amount is between about 0.10 and 0.45 mg/day. In a further embodiment the amount is between about 0.45 and 0.65 mg/day. In a still further embodiment the amount is between about 0.05 and 0.45 mg/day. In a further embodiment the amount is between about 0.10 and 0.65 mg/day. In a particular embodiment the amount is about 0.25 mg/day.

In a further embodiment of the present invention R in the compound of formula I is methyl.

In a still further embodiment of the present invention the compound of formula I is in the trans configuration.

In a further embodiment of the present invention the compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman or a salt thereof.

In a still further embodiment of the present invention the compound of formula I is an isolated l-enantiomer or a salt thereof.

In a further embodiment of the present invention the compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane or a salt thereof.

In a still further embodiment of the present invention the compound of formula I is in the form of the hydrogen fumarate salt.

In a further embodiment of the present invention the compound of formula I is in the form of the hydrogen maleate salt.

In a still further embodiment of the present invention the composition further comprises a hydrophilic binder, e.g. gelatin, cellulose derivative, cross-linked polyvinylpyrrolidone or copolyvidone, wherein the amount of hydrophilic binder in the pharmaceutical composition is preferably from about 1% to about 25% (w/w), more preferred from about 2,5% to about 15% (w/w). More preferably, the hydrophilic binder is polyvinylpyrrolidone or copolyvidone. Most preferably, the hydrophilic binder is copolyvidone.

In a further embodiment of the present invention the composition further comprises a water-soluble diluent, wherein the amount of water-soluble diluent in the pharmaceutical composition is preferably from about 20% to about 98% (w/w), more preferred from about 20% to about 80% (w/w). The water-soluble diluent is preferably a sugar, a polysaccharide or cyclodextrin. More preferably, the water-soluble diluent is a sugar, such as lactose, sucrose, dextrose. Most preferably, the water-soluble diluent is lactose.

In a still further embodiment of the present invention the composition further comprises a non water-soluble diluent, wherein the amount of non water-soluble diluent in the pharmaceutical composition is preferably from about 1% to about 50% (w/w), more preferred from about 5% to about 30% (w/w). The non water-soluble diluent is preferably a calcium phosphate, calcium sulphate, starches, modified starches or microcrystalline cellulose. The non water-soluble diluent is more preferably microcrystalline cellulose.

In a further embodiment of the present invention the composition further comprises an antioxidant, such as tocopherols or tocopherolesters, e.g. alpha-tocopherol succinate.

The composition is usually presented as a unit dose composition containing 0.01 -0.65 mg/day of a compound of formula I for oral dosing. The pharmaceutical compositions may be administered in a dosage form, preferably a unit dosage form, on a daily to weekly basis either once or divided in 2 or 3 doses, or 2 or 3 times per week or once weekly or once per 14 days.

In a still further embodiment of the present invention the composition may be on a solid dosage form, such as a tablet or capsule, or on a liquid dosage form, such as a solution, suspension or emulsion. Preferably, the composition is formulated as a tablet. For instance, such tablet may be administered on a daily basis, thus, comprising 0.01-0.65 mg of a compound of formula I, preferably levormeloxifene, more preferred levormeloxifene fumarate.

Optionally the composition further comprises a surfactant. When the surfactant is present, preferably it is an anionic or nonionic surfactant. Representative surfactants from this preferred group include sodium laurylsulfate, polyglycolyzed glycerides, polyoxyethylene sorbitan fatty acid esters, monoglycerides, diglycerides or glycerol. More preferably, the surfactant is a nonionic surfactant, such as polyoxyethylene sorbitan fatty acid esters or glycerol. Most preferably, the surfactant, when present, is glycerol.

Optionally the composition further comprises a lubricant(s) and/or a disintegrant.

In general, inhibition of bone loss is manifested as a statistically significant difference on cancellous bone volume between treatment and control groups. This can be seen as, for example, a 5-10% or more difference on spinal bone mass or bone mineral content over two years. Data from accepted animal models, such as the ovariectomized mouse or rat models of osteoporosis, are generally predictive of doses in humans to within one order of magnitude.

Within the present invention, the compounds of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, maleic acid tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The general chemical terms used in the above formula have their usual meanings.

As used herein, the term "C_{1-6}alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like.

The term "pharmaceutically acceptable salt" represents salt forms of a compound of formula I that are physiologically suitable for pharmaceutical use. The pharmaceutically acceptable salts can exist in conjunction with a compound of formula I as acid addition primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula I, wherein R is as defined previously. The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the metal hydroxide of the desired metal salt with a compound of formula I, wherein R is hydrogen.

The term "treating" or "treatment" is also intended to include prophylactic treatment.

The term "patient" is intended to include mammals, e.g. humans, such as males or females.

The term "hydrophilic binder" represents binders commonly used in the formulation of pharmaceuticals, such as polyvinylpyrrolidone, copolyvidone (cross-linked polyvinylpyrrolidone), polyethylene glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, tragacanth, guar, and alginates), gelatin, and cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethylcellulose).

The term "water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "non water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as a calcium phosphate, calcium sulphate, starches, modified starches or microcrystalline cellulose.

The term "surfactant", as used herein, represents ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids.

The term "antioxidant" represents the three groups of antioxidants, true antioxidants, reducing agents and antoxidant synergists, such as tocopherols, tocopherolesters, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, citric acid, edetic acid and its salts, lecithin and tartaric acid.

The term "disintegrant" represents compounds such as starches, clays, celluloses, alginates, gums, cross-linked polymers (such as cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose), sodium starch glycolate, low-substituted hydroxypropyl cellulose, and soy polysaccharides. Preferably, the disintegrant is a modified cellulose gum such as e.g. cross-linked sodium carboxymethylcellulose.

The term "lubricant" represents compounds frequently used as lubricants or glidants in the preparation of pharmaceuticals, such as talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, magnesium carbonate, magnesium oxide, calcium silicate, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, sodium laurylsulfate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably, the lubricant is magnesium stearate or talc, more preferably magnesium stearate and talc in combination.

The orally administerable formulations of the present invention are prepared and administered according to methods well known in pharmaceutical chemistry, see Remington's Pharmaceutical Sciences, 17th ed. (A. Osol ed., 1985). For example, the compositions of the present invention may be administered by means of solid dosage forms such as tablets and capsules. Preferably, the compositions are formulated as tablets. These tablets may be prepared by wet granulation, by dry granulation, or by direct compression.

Tablets for this invention are prepared utilizing conventional tabletting techniques. A general method of manufacture involves blending of a compound of formula I, or a

salt thereof, and optionally the water-soluble diluent, the non water-soluble diluent, hydrophilic binder and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant and milled, if necessary. The granules are dried and reduced to a suitable size. Any other ingredients, such as lubricants, (e.g. magnesium stearate) and additional disintegrants, are added to the granules and mixed. This mixture is then compressed into a suitable size and shape using conventional tabletting machines such as a rotary tablet press. The tablets may be film coated by techniques well known in the art.

Capsules for this invention are prepared utilizing conventional methods. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, and optionally the water-soluble diluent, the non water-soluble diluent, a hydrophilic binder, and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant in water, and milled, if necessary.

The granules are dried and reduced to a suitable size. Any other ingredients, such as a lubricant, are added to the granules and mixed. The resulting mixture is then filled into a suitable size hard-shell gelatin capsule using conventional capsule-filling machines.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLES

Levormeloxifene fumarate and maleate was synthesized, purified and crystallized as described in the following examples.

Example 1

(-)-3R,4R-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, hydrogen fumarate (levormeloxifene fumarate).

To a stirred, 50 °C warm, solution of (+/-) - trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane (1.00 kg, 2.19 mol) in methanol (10 l) was added (+)-ditoluoyltartaric acid (464 g, 1.20 mol). The suspension was stirred at 50 °C until the solution was homogenous.

Formic acid (73 g, 1.59 mol) was added to the solution and the temperature was allowed to drop to 30 - 40 °C. If the crystallization has not started at this point, the solution was seeded, and the temperature was allowed to drop further down to 20 °C. The suspension was stirred for two hours at 20 °C and then cooled down to 5 - 10°C for two hours and the crystals were collected by filtration. Yield 742 g.

Recrystallization from refluxing methanol (26 l) gave after cooling to 5-10 °C and filtration pure crystals of the levormeloxifene (+)-ditoluoyltartrate salt. Yield 556 g. M.p. 136 - 138 °C (dec.).

(-)-3R,4R-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, (+)-ditoluoyltartrate (500 g) was suspended in a mixture of toluene (2.5 l), water (2 l) and sodium carbonate (157 g) at ambient temperature. The mixture was stirred until the salts were dissolved. The aqueous phase was separated . The toluene phase was washed with water (2 l) and evaporated to an oil. The oil was dissolved in ethanol (1 l) at 40 - 60 °C and the solution was added to a solution of fumaric acid (69 g, 0.59 mol) in ethanol (2 l). The fumarate salt crystallized readily and

the mixture was stirred for an hour at 40 - 60 °C and then cooled down to 5 °C. The title compound was collected by filtration and dried at 50 °C to give 321 g (57 %).

M.p. 225 °C. (DSC).

^{1}H-NMR (DMSO-d_6, TMS): δ (ppm): 2.90 (4H,m), 1.75 (4H, m), 3.10 (2H,t), 4.06 (2H,t), 6.69 (2H,d), 7.01 (2H,d), 4.50 (1H,d), 6.44 (1H,m), 6.33(1H, m), 6.38(1H, m), 3.28(1H,d), 7.31(2H, br.s), 7.20(2H,m), 7.11(1H, m), 1.15(3H,s), 1.27(3H,s), 3,68(3H, s), 6.53(2H,s) 10.0(2H, s).

MS: 457.2632 (M^+ measured), 457.2617 (M^+ calculated)

Elemental Analysis: ($C_{30}H_{35}NO_3$,$C_4H_4O_4$), Calculated: C:71.18 %, H: 6.85 %, N: 2.44 %, Found: C: 71.23 %, N: 7.15 %, N: 2.31 %

Optical rotation: $[\alpha]^{20}_D$ = - 153.8 ° (c = 0.5 w/v % in ethanol).

Example 2

(-)-3R,4R-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, hydrogen maleate (levormeloxifene maleate)

To a stirred, 50 °C warm, solution of (+/-) - trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane (1.00 kg, 2.19 mol) in methanol (10 l) was added (+)-ditoluoyltartaric acid (464 g, 1.20 mol). The suspension was stirred at 50 °C until the solution was homogenous.

Formic acid (73 g, 1.59 mol) was added to the solution and the temperature was allowed to drop to 30 - 40 °C. If the crystallization has not started at this point, the solution was seeded, and the temperature was allowed to drop further down to 20 °C. The suspension was stirred for two hours at 20 °C and then cooled down to 5 - 10°C for two hours and the crystals were collected by filtration. Yield 742 g.

Recrystallization from refluxing methanol (26 l) gave after cooling to 5-10 °C and filtration pure crystals of the levormeloxifene (+)-ditoluoyltartrate salt. Yield 556 g. M.p. 136 - 138 °C (dec.).

(-)-3R,4R-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, (+)-ditoluoyltartrate (500 g) was suspended in a mixture of toluene (2.5 l), water (2 l) and sodium carbonate (157 g) at ambient temperature. The mixture was stirred until the salts were dissolved. The aqueous phase was separated . The toluene phase was washed with water (2 l) and evaporated to an oil.

A part of the oil (3 g, 0.0066 mole) was dissolved in toluene (60 ml). Maleic acid (0.8 g, 0.0066 mole) was added. The mixture was heated until homogenous. It was stirred over night at ambient temperature. The maleinate salt crystallized readily. The title compound was collected by filtration and dried at 50 °C to give 3 g (80 %).

The compound was identified by NMR and elemental analysis.

Formulation 1

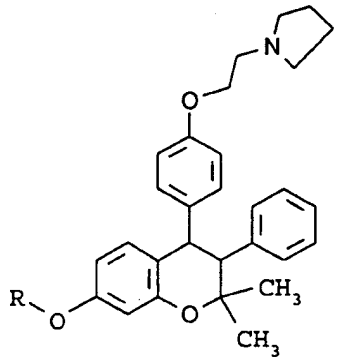
A typical tablet, which may be prepared by conventional tabletting techniques, contains:

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.313 mg
Microcrystalline Cellulose	12.00 mg
Cross-Carmellose Sodium	6.25 mg
Copolyvidone	6.00 mg
Lactose	54.20 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.40 mg
Talc	0.80 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 80 mg.

Claims

1. A pharmaceutical composition of a dosage form for oral administration comprising a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, in an amount of between about 0.01 and 0.65 mg/day .

2. The composition of any one of the above claims wherein R in the compound of formula I is methyl.

3. The composition of any one of the above claims wherein the compound of formula I is in the trans configuration.

4. The composition of any one of the above claims wherein the compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman or a salt thereof.

5. The composition of any one of the above claims wherein the compound of formula I is an isolated l-enantiomer or a salt thereof.

6. The composition of any one of the above claims wherein the compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane or a salt thereof.

7. The composition of claim 6 wherein the compound of formula I is in the form of the hydrogen fumarate salt.

8. The composition of any one of the above claims further comprising a hydrophilic binder.

9. The composition of any one of the above claims further comprising a water-soluble diluent.

10. The composition of any one of the above claims further comprising a non water-soluble diluent.

11. The composition of any one of the above claims further comprising an anti-oxidant.

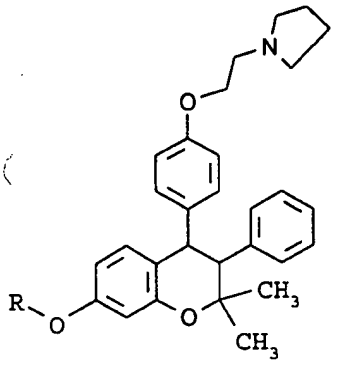
12. The composition of any one of the above claims further comprising a film coating.

13. The composition of any one of the above claims for reducing or preventing bone loss.

14. The composition of claim 13, wherein the bone loss is due to osteoporosis.

15. The composition of any one of the above claims, wherein said composition is formulated as a tablet.

16. Use of a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, in an amount of between about 0.01 and 0.65 mg/day, for the preparation of a pharmaceutical composition of a dosage form for oral administration for reducing or preventing bone loss.

17. Use according to claim 16, wherein the bone loss is due to osteoporosis.

18. Use according to any one of the above claims 16-17, wherein R in the compound of formula I is methyl.

19. Use according to any one of the above claims 16-18, wherein the compound of formula I is in the trans configuration.

20. Use according to any one of the above claims 16-19, wherein the compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman or a salt thereof.

21. Use according to any one of the above claims 16-20, wherein the compound of formula I is an isolated l-enantiomer or a salt thereof.

22. Use according to any one of the above claims 16-21, wherein the compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane or a salt thereof.

23. Use according to any one of the above claims 16-22, wherein the compound of formula I is in the form of the hydrogen fumarate salt.

24. Use according to any one of the above claims 16-23, wherein the composition further comprises a hydrophilic binder.

25. Use according to any one of the above claims 16-24, wherein the composition further comprises a water-soluble diluent.

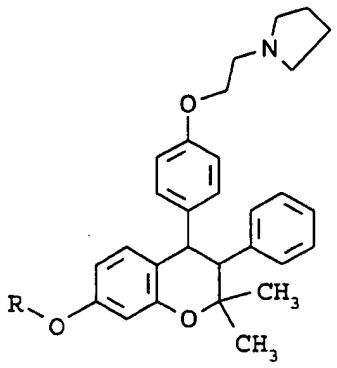
26. Use according to any one of the above claims 16-25, wherein the composition further comprises a non water-soluble diluent.

27. Use according to any one of the above claims 16-26, wherein the composition further comprises an antioxidant.

28. Use according to any one of the above claims 16-27, wherein the composition further comprises a film coating.

29. Use according to any one of the above claims 16-28, wherein the composition is formulated as a tablet.

30. A method for reducing bone loss in a patient comprising administering to the patient suffering from bone loss a composition of a dosage form comprising a bone loss inhibiting amount of between about 0.01 and 0.65 mg/day of a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof.

31. The method according to claim 30, wherein the bone loss is due to osteoporosis.

32. The method according to any one of the above claims 30-31, wherein R in the compound of formula I is methyl.

33. The method according to any one of the above claims 30-32, wherein the compound of formula I is in the trans configuration.

34. The method according to any one of the above claims 30-33, wherein the compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman or a salt thereof.

35. The method according to any one of the above claims 30-34, wherein the compound of formula I is an isolated l-enantiomer or a salt thereof.

36. The method according to any one of the above claims 30-35, wherein the compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane or a salt thereof.

37. The method according to any one of the above claims 30-36, wherein the compound of formula I is in the form of the hydrogen fumarate salt.

38. The method according to any one of the above claims 30-37, wherein the composition further comprises a hydrophilic binder.

39. The method according to any one of the above claims 30-38, wherein the composition further comprises a water-soluble diluent.

40. The method according to any one of the above claims 30-39, wherein the composition further comprises a non water-soluble diluent.

41. The method according to any one of the above claims 30-40, wherein the composition further comprises an antioxidant.

42. The method according to any one of the above claims 30-41, wherein the composition further comprises a film coating.

43. The method according to any one of the above claims 30-42, wherein the composition is formulated as a tablet.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00469

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9420098 A1 (ZYMOGENETICS, INC.), 15 Sept 1994 (15.09.94) --	1-29
X	US 4447622 A (MOHAMMAD SALMAN ET AL), 8 May 1984 (08.05.84) --	1-15
X	WO 9725038 A1 (NOVO NORDISK A/S), 17 July 1997 (17.07.97) --	1-15
P,X	WO 9823270 A1 (NOVO NORDISK A/S), 4 June 1998 (04.06.98) -- --------	1-29

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 1999	27 -02- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK98/00469

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 30-43
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

21/12/98

International application No.
PCT/DK 98/00469

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9420098 A1	15/09/94	AU 674394 B	19/12/96
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		US 5726202 A	10/03/98
WO 9823270 A1	04/06/98	AU 5049098 A	22/06/98